REMARKS/ARGUMENTS

The Present Invention

The present invention is directed to isolated cancer peptides or functionally equivalent variants thereof, compositions thereof, and immunogens comprising the same.

The Pending Claims

Claims 3, 5-8, 10, 14, 26, 28, 29, 67-77, 83-85, and 87-103 are pending.

The Amendments to the Specification and Claims

The specification at page 33, lines 3 and 14, has been amended to recite "HLA-A31^{+}" instead of "MHLA-A31" (in line 3) and "MHL-A31" (in line 14).

Claims 12, 13, and 15 have been canceled. Claim 3 has been amended to delete part (b), which is directed to optional additional contiguous amino acids of SEQ ID NO: 4, and has been amended to recite that the cancer peptide can consist of amino acids 52-62, 51-62, 50-62, 49-62, or 48-62 of SEQ ID NO: 4. Claims 7 and 96 have been amended to delete the recitation of "derived from" and has been amended to recite "is expressed by a cell of a cancer." Claims 8 and 97 have been amended to depend on claims 7 and 96, respectively. Claim 26 has been amended to be dependent on claim 3 and to delete all other descriptive language of the cancer peptide. Claim 69 has been amended to recite "functionally equivalent variant" instead of "isolated cancer peptide." Claim 72 has been amended to recite that the functionally equivalent variant consists of amino acids 53-62 of SEQ ID NO: 4 except that amino acid 53 of SEQ ID NO: 4 is substituted with a different amino acid. Claim 73 has been amended to correlate with the language of claim 72. Namely, claim 73 has been amended to recite "different amino acid" in lieu of "additional amino acid." Claim 85 has been amended to depend on claim 84 instead of claim 83. Claim 87 has been amended to delete "about." No new matter has been added by way of these amendments.

Discussion of the Enablement Rejection

The Office rejects claims 3, 5-10, 12-15, 26, 28, 29, 67-85, and 87-103 under 35 USC 112, first paragraph, as allegedly lacking enablement. Specifically, the Office argues that the specification does not teach any variant cancer peptide that contains an additional 1 to about 10 or 1 to about 5 additional contiguous amino acids of SEQ ID NO: 4 at the N-terminus of

the cancer peptide consisting of amino acids 127-136 of SEQ ID NO: 4, wherein the variant cancer peptide stimulates cytotoxic T lymphocytes. Also, the Office argues that the full scope of the variant cancer peptides consisting of amino acids 53-62 of SEQ ID NO: 4 are not enabled in view of the alleged limited disclosure of the cancer peptide variants that stimulate cytotoxic T lymphocytes. The rejection is traversed for the reasons set forth below.

Claim 9 was previously canceled. Claims 12, 13, and 15 have been canceled herein. Also, the language of claim 3 directed to additional contiguous amino acids of SEQ ID NO: 4 at the N-terminus of the cancer peptide has been deleted. Thus, the rejection as it pertains to these claims, or parts thereof, is moot.

Furthermore, the subject matter of claims 10, 14, 70, 71, 73-77, 89, 90, and 91 has been actually reduced to practice and the specification describes their production and use of such subject matter. It is, therefore, unclear why these claims are included in the rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent may be enabling even though some experimentation is necessary; the amount of experimentation, however, must not be unduly extensive. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

As set forth in the previously filed Amendment and Response to Office Action, the instant claims, when considered in view of the Wands factors, do not require undue experimentation.

In the instant case, the nature of the invention is an isolated cancer peptide consisting of (i) amino acids 53-62 of SEQ ID NO: 4, (ii) amino acids 127-136 of SEQ ID NO: 4, (iii) a functionally equivalent variant of (i) having at least 90% sequence identity to amino acids 53-62 of SEQ ID NO: 4, (iv) amino acids 52-62 of SEQ ID NO: 4, (v) amino acids 51-62 of SEQ

ID NO: 4, (vi) amino acids 50-62 of SEQ ID NO: 4, (vii) amino acids 49-62 of SEQ ID NO: 4, or (viii) amino acids 48-62 of SEQ ID NO: 4. The claimed cancer peptides and functionally equivalent variants thereof stimulate cancer antigen specific T lymphocytes.

The breadth of the claims is limited to those peptides *consisting of* one of seven specific portions of SEQ ID NO: 4, or variants thereof. The variants must have at least 90% sequence identity to amino acids 53-62 of SEQ ID NO: 4. The claimed peptides and variants are limited to those that stimulate cancer antigen specific T lymphocytes.

The originally-filed application provides an ample amount of direction provided by the inventor and several working examples, such that the level of predictability is reasonably high and the quantity of experimentation needed to make or use the invention based on the content of the disclosure is low. In particular, the specification at, for instance, page 31, lines 1-17, and page 44, line 1 through page 47, line 18, teaches a method of making and testing peptides and variants thereof for the ability to stimulate cancer antigen specific T lymphocytes. Over 20 specific peptides, including variants, were tested for the ability to stimulate T lymphocytes as measured by GM-CSF release. The results presented in Table 7 also provide teachings that one of ordinary skill in the art would take into consideration when making and testing other variants not explicitly set forth in Table 7. For instance, the results presented in Table 7 teaches that modification of a peptide at amino acid position 53 or 54 of SEQ ID NO: 4 with an aliphatic amino acid will yield a variant peptide that stimulates cancer antigen specific T lymphocytes. Table 7 also teaches that modification of a peptide at amino acid position 62 with a negatively-charged amino acid or a bulky aromatic amino acid will yield a variant peptide that does not stimulate cancer antigen specific T lymphocytes. The specification at page 10, lines 2-7, even provides a generic structural formula for a peptide variant that teaches how to make a peptide variant. Therefore, the originally-filed disclosure provides ample direction, including several working examples, such that one of ordinary skill in the art can predictability make a variant peptide without undue experimentation.

The level of one of ordinary skill, as evident by the prior art, is sufficient to make and use the instant invention. The art of making and testing peptides for antigenicity was well-known long before the filing date of the instant application (see Gill et al., *J Biol Chem* 242: 3308-3318 (1967)). The art of testing peptides for the ability to stimulate antigen specific T lymphocytes was known at least as early as November 1994 (see Estaquier et al., *Eur J Immunol* 24(11):2789-95 (1994), abstract).

The Office contends that Gill et al. and Estaquier et al. do not provide adequate evidence to support the full scope of the presently claimed cancer peptide variants. Specifically, the Office argues that Gill et al. is directed to the antigenicity of synthetic peptides and the factors that influence their ability to elicit antibodies, whereas the presently claimed invention is drawn to cancer peptides and stimulation of cytotoxic T lymphocytes. The Office further argues that Estaquier et al. does not provide any guidance with respect to MHC restriction, the ability of antigen specific stimulated cytotoxic T lymphocytes to faithfully mimic the naturally processed antigen, or whether the synthetic peptide variants will effectively stimulate CTLs that recognize tumor cells naturally expressing NY-ESO-1 in vivo.

However, Applicants did not provide Gill et al. to evidence that one of ordinary skill in the art was familiar with peptide-induced stimulation of cytotoxic T lymphocytes and did not provide Estaquier et al. to evidence all that the Office states that Estaquier et al. does not evidence, e.g., MHC restriction, etc. Rather, Gill et al. was provided to merely demonstrate that, as early as 1967, one of ordinary skill in the art was capable of making a peptide. Estaquier et al. was provided to merely demonstrate that, as early as 1994, the ordinarily skilled artisan was capable of testing a multitude of peptides for the ability to create a $CD8^+$ T cell response as measured by T cell responses, such as T cell proliferation and IL-2 production. Estaquier et al. was further provided to demonstrate that testing many peptides at once is within the skill of the ordinarily skilled artisan, since Estaquier et al. was able to test 7.5×10^5 peptides for the ability to induce a $CD8^+$ T cell response, a $CD4^+$ T helper cell response, and an antibody response all in one study.

The Office states on page 5 of the Office Action that Estaquier et al. confirms that additional experiments are necessary to discover those peptides that stimulate cancer antigen specific T lymphocytes. Applicants cannot find in the abstract of Estaquier et al. the statement(s) supporting this allegation, however, and request the Office to point out the specific statement(s) in Estaquier et al. upon which this allegation was made.

The Office contends that the specification fails to provide any specific guidance for producing and using the full scope of the cancer peptide variants. As stated above, sufficient guidance for carrying out the present inventive method is found in the specification at, for instance, Table 7, page 10, lines 2-7, page 47, lines 13-16, and page 53, lines 4-20.

It appears that the Office requires that the specification teach how to carry out every possible embodiment of the present invention. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*, 654 F.2d 103, 105, 210 UAPQ 689, 691 (CCPA 1981). "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." *In re Gay*, 309F.2d 769, 774, 50 CCPA 725, 733, 135 USPQ 311, 316 (CCPA 1962).

In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention *In re Wright*, 999F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by the claim is not adequately enabled by the disclosure). MPEP 2164.04

In the instant case, the Office cites to journal articles which allegedly demonstrate that even minor changes in the structure of an NY-ESO cancer peptide can alter the reactivities such that the cancer peptide may fail to stimulate cytotoxic T lymphcytes. The Office points to Table 7 in support of arguing that not all cancer peptide variants would work.

However, as stated herein, the specification teaches, for example, which residues of the cancer peptide are important and which may be replaced (*see*, for example, Table 7). Thus, the unpredictability of the results of certain species of the claimed genus of cancer peptides is removed by such teachings.

The Office states on page 7 of the Office Action that reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Reasonable detail of the claimed variant cancer peptides which stimulate cytotoxic T lymphocytes is set forth in the instant specification, as outlined herein. Thus, the instant specification does, in fact, provide working examples which provide evidence that are reasonably predictive of cancer peptides not explicitly disclosed in the instant specification.

In view of the foregoing, the claimed invention is enabled by the instant specification. Thus, the rejection is requested to be withdrawn.

Discussion of the Objection to the Specification

The Office objects to the specification for the recitation of "MHLA-A31" on page 33, line 3, and "MHL-A31" on page 33, line 14. The specification has been amended to recite "HLA-A31" in both instances. Thus, the objection to the specification is moot.

Discussion of the Objection to the Claims

The Office objects to claims 13, 72, and 87 under 37 CFR 1.75 (c), as allegedly being in improper dependent form. Specifically, the Office argues that none of the rejected claims further limit the scope of claim 3. Claim 13 has been canceled. Thus, the objection as it pertains to this claim is moot. Claim 72 has been amended to be directed to functionally equivalent variants consisting of amino acids 53-62 of SEQ ID NO: 4 except that amino acid 53 of SEQ ID NO: 4 is substituted with a different amino acid. Claim 87 has been amended to delete "about." As amended herein, claims 72 and 87 limit the scope of claim 3, such that the claims properly depend from claim 3. The withdrawal of the objection to the claims is therefore requested.

Discussion of the Indefiniteness Rejection

The Office rejects claims 7 and 96 under 35 USC 112, first paragraph, as allegedly indefinite. Specifically, the Office alleges that the recitation of "derived from" in claims 7 and 96 renders the claim unclear. Claims 7 and 96 have been amended to delete the phrase "derived from" and to recite that the cancer peptide "is expressed by a cell of a cancer" which is supported by the specification at, for instance, page 8, lines 4-20. In view of the amendments to the claims, claims 7 and 96 are definite. Accordingly, the withdrawal of the indefiniteness rejection is requested.

Discussion of the Written Description Rejection

Claims 3, 5-8, 12, 26, 28, 29, 67-69, 72, 83-85, 87, 88, and 92-103 are rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office specifically argues that the specification does not disclose or provide adequate written description of the genus of isolated cancer peptides consisting of amino acids 53-62 or 127-136 of SEQ ID NO: 4 and containing additional contiguous amino acids at the N-terminus of the isolated cancer peptide. The species of cancer peptides disclosed in Table 7 of the instant specification allegedly are insufficient to constitute a representative number of species, because the genus is allegedly highly variable and one of ordinary skill in the art could not predict the operability in the invention of any species other

than the peptides disclosed in the specification. This rejection is traversed for the numerous reasons set forth below.

Claim 3 has been amended to delete the language directed to additional contiguous amino acids of SEQ ID NO: 4 at the N-terminus of the cancer peptide. Also, claim 12 has been canceled. Thus, the rejection as it pertains to this part of claim 3 and all of claim 12 is moot.

The Office quotes *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004) and *Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d at 966, 63 USPQ2d at 1615 (Fed. Cir. 2002) when arguing that the number of species of cancer peptides disclosed in Table 7 is an insufficient number to represent the claimed genus. The Office quotes *Curtis* as stating: "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when...the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed" and quotes *Enzo* as stating: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."

As a first matter, *Curtis* does not apply to the instant case, because Table 7 discloses more than a *single* species of the claimed genus. Table 7 discloses, for example, SEQ ID NOs: 34-38, 41, and 42, all of which are species of the claimed genus.

Further, *Enzo* does not apply to the instant case, because the data disclosed in the instant specification evidence predictability in the results obtained from species other than those specifically enumerated, and the data allow the ordinary artisan to predict the operability in the invention of species other than those disclosed. Table 7, for instance, teaches that an aliphatic amino acid could replace the amino acid at position 2 of the peptide consisting of amino acids 53-62 of SEQ ID NO: 4, since Table 7 discloses that cancer peptides with Ser, Ala, Ile, Leu, Val, or Thr, all of which are aliphatic amino acids, at position 2 of the cancer peptide consisting of amino acids 53-62 of SEQ ID NO: 4 stimulate cancer antigen specific T lymphocytes as indicated by cytokine release by cytotoxic T lymphocytes.

Also, Table 7 teaches that substituting an amino acid at position 10 of the cancer peptide consisting of amino acids 53-62 of SEQ ID NO: 4 would not yield a cancer peptide

which stimulates cancer antigen specific T lymphocytes, since substitution with a similar amino acid at this position caused the peptide to lose activity. Further, the specification at page 47, lines 13-16, states that this residue represents a critical anchor residue.

The specification at page 53, lines 4-20, further teaches ordinarily skilled artisans which residues of the claimed cancer peptides are important for binding to an MHC molecule. For instance, the specification teaches that the prolines allow the peptides to fit into the binding pocket of the MHC molecule.

Therefore, the teachings of the instant specification evidence predictability of the results obtained from species not explicitly disclosed by the specification.

The Office also cites several journal articles in arguing that protein chemistry is one of the most unpredictable areas of biotechnology. However, as stated herein, the instant specification teaches, for example, which residues of the cancer peptide are important and which residues can be replaced, such that unpredictability in the results obtained from species other than those specifically enumerated is removed.

In view of the foregoing, the specification provides one of ordinary skill in the art with the ability to predict the operability of species other than those that are explicitly disclosed. Accordingly, *Curtis* and *Enzo* cannot be used as a basis for arguing that the number of species of cancer peptides disclosed in Table 7 is an insufficient number to represent the claimed genus.

The Office states on page 13 of the Office Action: "Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required." Also, on page 15, the Office states "the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of cancer peptide variants, and therefore conception is not achieved until reduction to practice has occurred." Further, when paraphrasing *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993), the Office states on page 15 of the Office Action that "adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required."

However, *Fiers*, 25 USPQ2d 1601 at 1606 (CAFC 1993) actually states: "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; *what is required is a description of the DNA itself.*" *Fiers*, 25 USPQ2d at 1606 (emphasis added).

Based on the Office's statements that "isolation and characterization at a minimum are required" and "conception is not achieved until reduction to practice has occurred" and on the stated interpretation of *Fiers*, it appears that the Office requires that Applicants actually reduce to practice, or isolate and characterize, each and every species of the claimed genus. This, however, is not required by the law.

The law, as set forth in *Fiers*, instead teaches that the written description requirement of 35 USC 112 for a claimed DNA sequence is satisfied by including a precise definition of the claimed DNA, such as by *structure, formula, chemical name, or physical properties*. *Fiers*, 25 USPQ2d at 1606. For the reasons set forth below, Applicants have met the written description requirement.

Further, although not binding law, the Board of Patent Appeals and Interferences (BPAI) found in Appeal No. 2003-1993 of Application No. 09/470,526, that the written description was met for a claimed polynucleotide having at least 80% identity to the entire coding region of a particular nucleotide sequence, even though the specification did not disclose a nucleotide sequence of a single species of the claimed genus of polynucleotides. The BPAI stated: "to satisfy the written description requirement it is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented the claimed subject matter. Thus, we do not find the fact that the specification does not specifically teach the structure of a species with 80% identity and WEE1 function to be dispositive of the written description issue here."

In the instant case, the instant specification provides *both* structural *and* functional descriptions of the claimed variant cancer peptides. Namely, the cancer peptides have at least 90% sequence identity to amino acids 53-62 of SEQ ID NO: 4 (ASGPGGGAPR) *and* stimulate cancer antigen specific T lymphocytes. Thus, the instantly claimed cancer peptides meet the written description requirement based upon the law, as set forth by *Fiers*.

Furthermore, the specification provides several species of the claimed genus and further teaches which residues are important for the function of the cancer peptide, as well as which residues may be substituted, such that one of ordinary skill in the art would recognize from these disclosures that applicants invented the claimed subject matter, as was the case in Appeal No. 2003-1993 of Application No. 09/470,526.

least 90% sequence identity to amino acids 53-62 of SEQ ID NO: 4 is evident from the disclosures of the instant application. For example, the specification at, for instance, Table 7, discloses several species of the claimed genus. Also, on page 7, lines 24-26, the specification states that the invention encompasses cancer peptide variants, and Table 7 implicitly supports cancer peptide variants that have at least 90% sequence identity to amino acids 53-62 of SEQ ID NO: 4. Therefore, the specification supports that the claimed cancer peptide variants were conceived.

In view of the foregoing, the specification of the instant application meets the written description requirement for the invention now claimed. Accordingly, it is hereby requested that the written description rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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